Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution for injection contains 2 mg epirubicin hydrochloride.

One 5 ml vial of Epirubicin 2 mg/ML solution for injection contains 10 mg epirubicin hydrochloride equivalent to 9.35 mg epirubicin.

One 10 ml vial of Epirubicin 2 mg/ml solution for injection contains 20 mg epirubicin hydrochloride equivalent to 18.7 mg epirubicin.

One 25 ml vial of Epirubicin 2 mg/ml solution for injection contains 50 mg epirubicin hydrochloride equivalent to 46.75 mg epirubicin.

One 50 ml vial of Epirubicin 2 mg/ml solution for injection contains 100 mg epirubicin hydrochloride equivalent to 93.5 mg epirubicin.

One 100 ml vial of Epirubicin 2 mg/ml solution for injection contains 200 mg epirubicin hydrochloride equivalent to 187 mg epirubicin.

Excipient with known effect: Contains sodium 3.54 mg/ml (0.154 mmol) (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epirubicin is used in the treatment of a range of neoplastic conditions including:
- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:
- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ of the bladder
- Prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Posology
Epirubicin is for intravenous or intravesical use only.

Paediatric population

There is a lack of data on safety and efficacy in children.

Intravenous administration
It is advisable to administer Epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see Section 4.4). In case of extravasation the administration should be immediately stopped.

Conventional dose
When epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body area. Epirubicin hydrochloride should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematomedullary status.
If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose
Epirubicin hydrochloride as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:
– Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.
For high dose treatment, epirubicin hydrochloride may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

Breast Cancer
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin hydrochloride ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m^2 for conventional treatment and 105-120 mg/m^2 for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

The following doses of epirubicin hydrochloride are commonly used in monotherapy and combination chemotherapy for various tumours, as shown:

	Epirubicin hydrochloride dose (mg/m^2)[a]	
Cancer Indication	**Monotherapy**	**Combination Therapy**
Advanced ovarian cancer	60–90	50–100
Gastric cancer	60–90	50
SCLC	120	120
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	

[a] Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy
If epirubicin hydrochloride is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function
The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin or SGOT levels as follows:

Moderate liver impairment (bilirubin: 1.4-3 mg/100ml) requires a 50% reduction of dose, while severe impairment (bilirubin> 3 mg/100 ml) necessitates a dose reduction of 75%.

SGOT*)	**Dose reduction**
2-5 x upper normal limit	50%
>5 x upper normal limit	75%

*) Serum glutamic oxaloacetic transaminase

Impaired renal function
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. Dose adjustments may still be necessary in patients with serum creatinine >5mg/dl.

Intravesical administration
Epirubicin hydrochloride can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see section 4.3). Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:

Once weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water) for 8 weeks. If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ: Up to 80 mg/50 ml (depending on individual tolerability of the patient).

For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

Dilution table for bladder instillation solutions

Dose epirubicin hydrochloride required	**Volume of 2 mg/ml epirubicin hydrochloride injection**	**Volume of diluent sterile water for injection or 0.9% sterile saline**	**Total volume for bladder installation**
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be retained intravesically for 1-2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

4.3 Contraindications

Epirubicin is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypersensitivity to other anthracyclines or anthracenediones.
- Lactation.

Intravenous use:
- Persistent myelosuppression.
- Marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or

radiotherapy.
- Previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines (e.g. doxorubicin or daunorubicin) and anthracenediones (see section 4.4).
- Current or previous history of cardiac impairment, including:
  - New York Heart Association (NYHA) class IV heart failure,
  - acute myocardial infarction and previous myocardial infarction with residual NYHA class III or class IV heart failure,
  - acute inflammatory heart disease,
  - arrhythmia with serious haemodynamic consequences.
- Unstable angina pectoris.
- Myocardiopathy.
- Acute systemic infections.
- Severe hepatic impairment.

Epirubicin is contraindicated for intravesical administration in case of:
- Urinary tract infections.
- Hematuria.
- Invasive tumours penetrating the bladder.
- Catheterisation problems.
- Inflammation of the bladder.

4.4 Special warnings and precautions for use

General: Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of cytotoxic therapy. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Patients should recover from acute toxicities (such as severe stomatitis or mucositis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin (e.g., ≥90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m^2 every 3 to 4 weeks) the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin does require special attention for possible clinical complications due to profound myelosuppression.

Cardiac Function: Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., acute) events: Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin treatment.

Late (i.e., delayed) events: Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug. Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment.

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly (see section 5.1).
An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment.
Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques. ECG changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or a specific method for following anthracycline-related cardiotoxicity.

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzamab therapy alone or in combination with anthracyclines such as epirubicin. This may be moderate to severe and has been associated with death, Trastuzumab and anthracyclines such as epirubicin should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of traztuzumab and anthracyclines.

Because the half-life of trastuzumab is approximately 28-38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function should be monitored carefully.

If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin therapy, it should be treated with the standard medications for this purpose.

The risk of serious cardiac impairment may be decreased through regular monitoring of the left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin with the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with ECG and MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin should be exceeded only with extreme caution.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section 4.5) with an increased risk in the elderly.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses (<900 mg/m^2) whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive. In the case of cardiac insufficiency the treatment with epirubicin should be discontinued.

Reproductive system: Epirubicin can have genotoxic effects. Therefore male patients treated with epirubicin are advised

to use effective contraceptive methods and if appropriate and available, seek advice regarding conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.

Female patients should not become pregnant during treatment with epirubicin. Males and females treated with epirubicin should use an effective method of contraception. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see section 4.6).

Effects at site of injection: Phlebosclerosis may result from injection into small vessels or repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

Extravasation: Extravasation of epirubicin during intravenous injection may cause local pain, severe tissue lesions (vesication, severe cellulites) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately discontinued. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (please refer to relevant labels for use). The patient's pain may be relieved by cooling down the area and keeping it cool, use of hyaluronic acid and DMSO. The patient should be monitored closely during the subsequent period of time, as necrosis may occur several weeks after extravasation occurs. If necessary, a plastic surgeon should be consulted with a view to possible excision.

Hematologic toxicity: As with other cytotoxic agents, epirubicin may produce myelosuppression. During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug.
Leukopenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia (<100,000 platelets/mm^3) and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary leukemia: Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period (see section 5.1).

Tumor-lysis syndrome: As with other cytotoxic agents, epirubicin may induce hyperuricaemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should therefore be evaluated after initial treatment so that this phenomenon may be recognised and properly managed. Hydration, urine alkalisation and prophylaxis with allopurinol to pevent hyperuricaemia may minimize potential complications of tumor-lysis syndrome.

Immunosuppressant effects/increased susceptibility to infections: Administration of live or live−attenuated vaccines in patients immunocompromised by chemotherapeutic agents including
epirubicin, may result in serious or fatal infections (see section 4.5). Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gastrointestinal: Epirubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver function: Epirubicin is mainly eliminated via the liver. Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (AST, SGT, alkaline phosphatase, serum total bilirubin). Patients with decreased liver function may experience slower clearance of drug with an increase in overall toxicity. For

these patients a dose reduction is recommended (see section 4.2 and 5.2). Patients with severe hepatic impairment should not receive epirubicin (see section 4.3).

Renal function: Serum creatinine levels should be checked regularly prior to and during treatment. For patients with increased serum creatinine (>5 mg/dl) a dose reduction is proposed (see section 4.2).

Other: As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of epirubicin.

Epirubicin may impart a red colour to the urine for one or two days after administration.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route: Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., uretheral obstruction due to massive intravesical tumors).

Intra-arterial route: Intra-arterial administration of epirubicin (transcatheter arterial embolization for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Epirubicin contains 3.54 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastro-intestinal effects (see section 4.4). The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs (e.g. 5−fluorouracil, cyclophosphamide, cisplatin, taxanes) or concomitant (or prior) radiotherapy to the mediastinal area, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section 4.4).

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites, when administered immediately after epirubicin.

The co-administration of interferon α_2b may cause a reduction in both the terminal elimination half life and the total clearance of epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites (e.g., epirubicinol), the latter being, however, neither toxic nor active.
Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane. One study has shown that paclitaxel clearance is reduced by epirubicin.
This combination may be used if using staggered administration between the two agents.
Infusion of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the two agents.

Quinine may accelerate the initial distribution of epirubicin from blood in to the tissues and may have an influence on the red blood cells partitioning of epirubicin.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m^2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter $p<0.05$). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity. Administration of cimetidine should be discontinued during treatment with epirubicin.

The possibility of a marked disturbance of haematopoiese needs to be kept in mind with a (pre-) treatment with agents which influence the bone marrow (i.e. cytostatic agents, sulphonamide, cloramphenicol, diphenylhydantoin, amidopyrinedervatives, antiretroviral agents).

Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

4.6 Fertility, pregnancy and lactation

Pregnancy
Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods.

Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman (see section 5.3). If epirubicin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the possibility of genetic counselling should be considered. There is no conclusive information as to whether epirubicin may cause teratogenesis. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals (see section 5.3). There are no studies in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding
It is not known whether epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from epirubicin, mothers should discontinue nursing prior to taking this drug.

Fertility
There is no conclusive information as to whether epirubicin may adversely affect human fertility. Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods and if appropriate and available, seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

4.7 Effects on ability to drive and use machines

The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated. Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of the ability to drive or operate machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

More than 10% of treated patients can expect to develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal side effects, anorexia, alopecia, infection.

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Common	Infection.
	Not known	Pneumonia, sepsis and septic shock may occur as a result of myelosuppression.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Acute lymphocytic leukaemia, acute myeloid leukaemia. Secondary acute myeloid leukaemia with or without a pre-leukaemic phase in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemia's have short (1-3 years) latency.
Blood and lymphatic system disorder	Very common	Myelosuppression* (leukopenia, granucytopenia and neutropenia, anemia and febrile neutropenia).
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur.
Immune system disorders	Common	Allergic reactions after intravesical administration.
	Rare	Anaphylaxis (anaphylaxis/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).
Metabolism and nutrition disorders	Common	Anorexia, dehydration.
	Rare	Hyperuricaemia (as a result of rapid lysis of neoplastic cells) (see section 4.4).
Nervous system disorders	Uncommon	Headache.
	Rare	Dizziness.
Eye disorders	Not known	Conjunctivitis, keratitis.
Cardiac disorders	Rare	Cardiotoxicity (ECG abnormalities, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusion, gallop rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block) (see section 4.4).
Vascular disorders	Common	Hot flashes.
	Uncommon	Phlebitis, thrombophlebitis.
	Not known	Shock, coincidental cases of thromboembolic events (including pulmonary embolism (in isolated cases with fatal outcome)) have occurred.
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Mucositis (may appear 5-10 days after the start of

		treatment and usually involves stomatitis with areas of painful erosions, ulceration and bleedings, mainly along the side of the tongue and the sublingual mucosa), stomatitis, oesophagitis and hyperpigmentation of the oral mucosa may also occur.
	Not known	Oral pain, mucosal burning sensation
Skin and subcutaneous tissue disorders	Very common	Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
	Uncommon	Hyperpigmentation of skin and nails, erythema, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction).
	Rare	Urticaria.
	Not known	Local toxicity, rash, itch, skin changes, flushing.
Renal and urinary disorders	Very common	Red coloration of urine for 1 to 2 days after administration.
Reproductive system and breast disorders	Rare	Amenorrhea, azoospermia.
General disorders and administration site conditions	Common	Redness along the infusion vein. Local phlebitis, phlebosclerosis. Local pain and tissue necrosis may occur (following accidental paravenous injection).
	Rare	Fever, chills, hyperpyrexia, malaise, weakness.
	Not known	Severe cellulitis
Investigations	Rare	Change in transaminase levels.
	Not known	Asymptomatic drops in left ventricular ejection fraction.
Injury, poisoning and procedural complications	Common	Chemical cystitis, in some cases haemorrhagic, has been observed following intravesical administration (see section 4.4).

*High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Intravesical administration:
As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria).Occasional bacterial or chemical cystitis have been reported (see section 4.4). These ADRs are mostly reversible.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia) within 10 - 14 days, gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Delayed cardiac failure has been seen with the anthracyclines several months to years after completion of treatment (see section 4.4). Patients should be observed carefully and should, if signs of cardiac failure arise, be treated according to conventional guidelines.

Treatment:
Symptomatic. Treatment should aim to support the patient during this period and should utilise such measures as antibiotica, blood transfusion and reverse barrier nursing. Epirubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances, ATC code: L01D B03

The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 is the limit for dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

In a pharmacokinetic study of patients with carcinoma in situ in the bladder the plasma levels of epirubicin after intravesical administration are typically low (<10 ng/ml). A significant systemic resorption is therefore not presumed. In patients with mucous membrane lesions in the bladder (e.g. tumour, cystitis, operations) an increased resorption rate may be expected.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged drug.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The drug does not cross the blood brain barrier.

5.3 Preclinical safety data

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, gastrointestinal tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.

A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

Prolonged contact with any solution of an alkaline pH (including bicarbonate containing solutions) should be avoided as it will result in hydrolysis of the drug. Only the diluents detailed in section 6.6 should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs. A physical incompatibility with heparin has been reported.

Epirubicin should not be mixed with other drugs.

6.3 Shelf life

Shelf life of the product as package for sale:
3 years

Shelf life after first opening the container:
The vials are for single use only and any unused portion must be discarded after use. From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

Shelf life after dilution of the solution for injection:
The product should be used immediately first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
For storage conditions after first opening and dilution of the medicinal product, see section 6.3.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Glass vial (type I) with bromobutyl rubber stopper and metallic cap (aluminium) with polypropylene disk. Epirubicin 2mg/ml Solution for Injection vial will be packed with or without a protective plastic overwrap.

Pack sizes:
1 x 5 ml vial (10 mg/5 ml)
1 x 10 ml vial (20 mg/10 ml)
1 x 25 ml vial (50 mg/25 ml)

1 x 50 ml vial (100 mg/50 ml)
1 x 100 ml vial (200 mg/100 ml)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Intravenous administration: It is advisable to administer Epirubicin 2mg/ml Solution for Injection via the tubing of a free-running intravenous saline infusion (see section 4.2).

Intravesical administration: Epirubicin 2mg/ml Solution for Injection should be diluted in sterile water for injection or 0.9% sterile saline solution before administration (see section 4.2).

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.

2. Preparation of an infusion solution should be performed in a designated aseptic area.

3. Adequate protective disposable gloves, goggles, gown and mask should be worn.

4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.

5. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.

6. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.

7. Pregnant staff should not handle the cytotoxic preparation.

8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group hf.
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1366/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th April 2008

Date of last renewal: 25th November 2012

10 DATE OF REVISION OF THE TEXT

November 2015